Neoplasia of the Large Intestine

Introduction

Colon cancer is ranked third in cancer incidence and cancer mortality (skin cancers excluded). Yet colon cancer is entirely preventable. We can prevent colon cancer by reducing risk factors and screening early. Almost all colon cancers progress from normal mucosa through a premalignant lesion, and only then on to malignancy. This process takes about 10 years. Screening and removal of premalignant lesions eliminate the risk of those lesions ever turning malignant. With colon cancer, we aren't just able to detect cancer early; we're able to prevent it altogether. Patients with lesions are screened more frequently. But the point is, if we get everyone screened appropriately, we can prevent colon cancer.

We are going to talk about the genetic mechanisms that give rise to colon cancer. More than for any other type of cancer, medical science has elucidated a recurring pattern in the development of colon cancer. Mutations are acquired in sequential order, each mutation leading to a more proliferative or dysplastic tumor. The familial syndromes that lead to colon cancer are those involving heritable defects along this sequence of mutations. We'll briefly discuss the clinical and epidemiologic features of colon cancers, with a glance at some nonmalignant polyps of the GI tract. We close with anal cancer, a cancer of squamous cell epithelium derived from ectoderm.

Polyps

First, a discussion on polyps. In clinical practice, we screen for colon cancer to detect premalignant lesions. Screening is done with **colonoscopy every 10 years** starting at **age 50** (younger for some, but learn this as the default). The reason to do colonoscopy is to find and remove polyps in the premalignant stage, preventing cancer from forming in the first place. Not all polyps are premalignant. The difficulty is that, as an endoscopist, the operator isn't able to predict whether a little bump is going to be malignant or not. So, all polyps should be removed, and that question should be answered by a pathologist. Although the shape of the polyp does not always correlate with the genetic progression (cancer can do what it wants), you should learn that microsatellite instability polyps take on the **serrated** morphology, whereas adenoma-carcinoma sequence polyps take on the **adenomatous** morphology. Any polyp is removed and evaluated for malignancy or malignant potential. Although **nothing matters more than the stage of cancer** in determining prognosis and treatment, there are certain features of the polyp that make it higher risk than others—pedunculated vs. sessile, small vs. large, and tubular vs. villous.

On colonoscopy, a **pedunculated** polyp is easy for an endoscopist to grab, and, having a stalk, the pathologist can be more certain that the stalk is clear of any dysplastic transformation. A **sessile** polyp is flat. It is more difficult to ensure that the entire polyp has been removed and more difficult to assess its margins. On histology, a polyp may be villous or tubular. The large intestine's epithelium is simple columnar and forms crypts (also called glands, also called invaginations), but don't form villi. The invagination-only normal epithelium is described as tubular. **Tubular** is the **normal structure** of the intestinal epithelium. Thus, tubular polyps tend to have a lower cancer risk. **Villous** histology is the presence of . . . you guessed it, villi, where the cancer grows up into the lumen from the tubular base. The small intestine has villi; the colon does not. Thus, when tissue behaves poorly (colon growing villi like the small intestine), it is usually a marker for altered gene expression, the same pathogenesis of malignancy. Tubular polyps are low-risk, whereas villous polyps are high-risk. The last thing to consider is **size**. The larger the polyp, the more likely there could be cancer hiding in it.

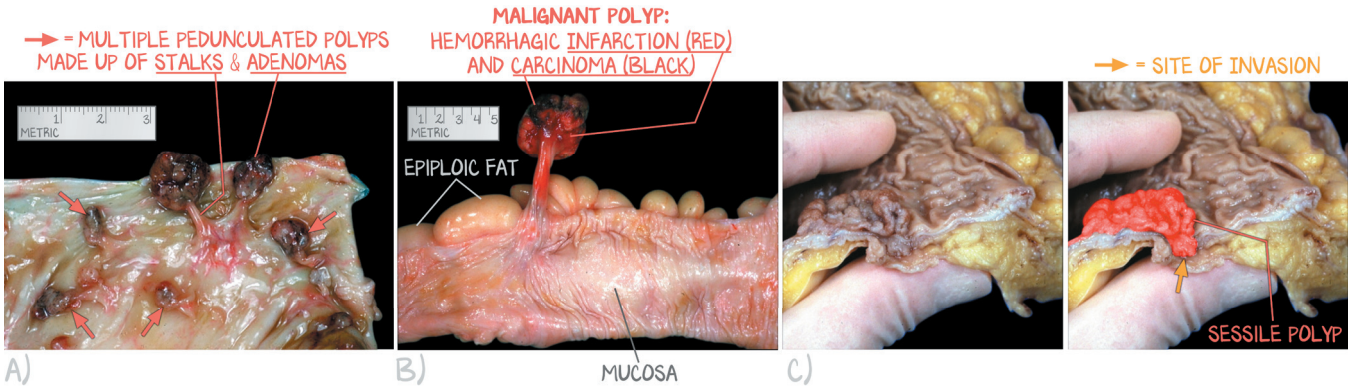

Figure 12.1: Polyps On Gross Examination
(a) Multiple, small, pedunculated polyps with stalks that extend from the mucosa to clumps at their tips. The proliferation occurs within the clumps. The stalks are a product of their extension into the lumen. (b) Large pedunculated polyp arising from the mucosa of this dissected colon, as evidenced by the rugae on the anterior surface and the epiploic fat seen posterior. The red color is due to a hemorrhagic infarction, whereas the brown-black at the polyp's end is due to adenocarcinoma. (c) Sessile polyps are easily missed, the rugae of the normal colon nearby very close in appearance to the pathologic polyp. This polyp was malignant, as evidenced by its invasion into the epiploic fat.

Large, villous, sessile polyps are **bad**. Small, tubular, pedunculated polyps are good (as good as a polyp can be, since all are pathologic, whereas some are at least not malignant). Nothing has a better prognostic value than the depth of invasion and cancer staging. But these "good" and "bad" features help orient new learners to the various elements that go into consideration.

HIGH-RISK FEATURE	FEATURE	LOW-RISK FEATURES
Villous	Shape	Tubular
> 2 cm	Size	< 2 cm
Sessile, flat	Gross Appearance	Pedunculated

Table 12.1: Features of High- and Low-Risk Polyps

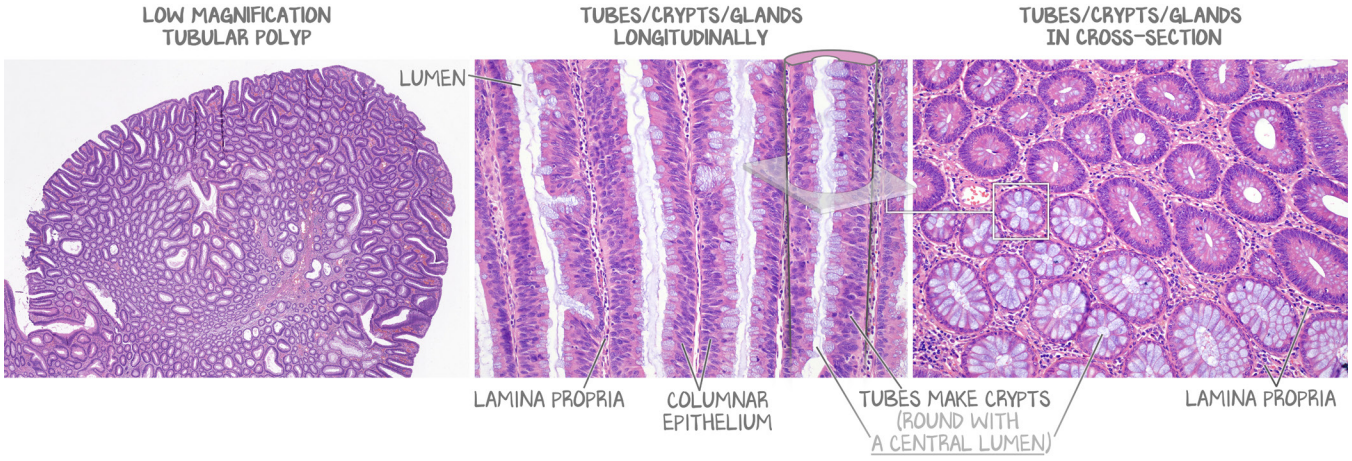

Figure 12.2: Histological Tubular Adenomas
"Tubular adenoma" describes the excessive proliferation of crypt-forming cells. Yep, "tubular" means "forms tubes" or "forms glands" or "the colon's normal histological arrangement." Crypts, glands, and now tubular growth are all defined as a simple columnar epithelium that invaginates into the lamina propria – crypts, glands, ducts, all the same thing. On longitudinal section, the central lumen gives the appearance of papillae—a small band of lamina propria with columnar cells on either side. These are not papillae, there is just such an abundance of invaginations that two come up, abutting one another so close together that the epithelia appear to share a lamina propria. They don't. The columnar cells on one side of the lumen share the cells of the epithelium across the lumen, not across the lamina propria. When seen in cross-section, these crypts/tubes/glands are circular structures with a central lumen surrounded by columnar cells, some secreting mucin, and others resembling the absorptive enterocytes. On longitudinal section, many nuclei are seen arising from the lamina propria, having lost its simple columnar designation, indicative of a growth more closely resembling carcinoma than that seen on cross-section. The low-magnification view shows invaginations from the surface, forming many glands/crypts/tubules with nearly no recognizable pattern.

Genetic Mechanisms of Colon Cancer

There are two main pathways by which colon cancer is initiated—the adenoma-carcinoma sequence and the microsatellite instability pathway. The adenoma-carcinoma sequence develops pedunculated, adenomatous polyps as premalignant lesions then progresses to adenocarcinoma of the colon. The microsatellite instability pathway develops serrated, sessile polyps as premalignant lesions then progresses to adenocarcinoma of the colon. Same outcome, different ways of getting there based on which gene mutation occurs first.

We will use our understanding of this colon cancer progression to predict what happens in familial polyposis syndromes (genetic diseases that result in polyps).

Adenoma-Carcinoma Sequence

The adenoma-carcinoma sequence will demonstrate the phenotype of pedunculated tubular adenoma, which then progresses on to adenocarcinoma. It starts with an adenomatous polyp.

An adenomatous polyp is premalignant, and a premalignant lesion will, by definition, become cancer if it's left alone. The sequence of gene mutations that takes the normal colon to adenocarcinoma is well established and accounts for 80% of all colon cancer. The sequence is implied by the frequency with which a mutation is expressed in nonmalignant polyps and carcinoma—mutations that are frequently found in polyps are early in the sequence; those found only in advanced-stage carcinomas are likely at the end of the sequence. The adenoma-carcinoma sequence begins with a **loss-of-function** mutation in **APC**. APC normally facilitates the degradation of β-catenin. β-Catenin is a signal for proliferation. The loss of APC allows β-catenin to accumulate, translocate to the nucleus, and promote the transcription of cyclins. The downstream effect is cell proliferation. Because almost 100% of carcinomas and adenomas of the adenoma-carcinoma sequence phenotype have the APC mutation (and the ones that don't have

some other β-catenin pathway mutation with similar effects), it is presumed to be the first mutation acquired. There is not yet an adenoma. The mucosa looks normal. There is nothing to biopsy. But the sequence has started.

With upregulated proliferation, there is more opportunity for more mutations. The upregulation of **COX-2** is found in 90% of carcinomas and 40% of adenomas. COX-2 produces PGE_2, which promotes angiogenesis. Aspirin inhibits COX-2. In retrospective analyses of patients with heart disease, those on aspirin had a decreased incidence of colorectal cancer. Since then, prospective studies have shown that **aspirin may be chemoprotective against colorectal cancer.** By the time COX-2 is upregulated, the polyp is easily identified. It grows into the lumen but is not dysplastic. Transformation is underway, but not obvious.

The next key mutation is in ***KRAS***, a member of the Ras oncogene family, which prevents apoptosis. *KRAS* mutations are found in 10% of small polyps and 50% of carcinomas, implying that it may be one of the key mutations that cause malignant transformation. The adenoma is still obvious, but a resection will reveal dysplasia. There may be invasion, or there may not be, but the cells are cancerous. Negative margins mean cure; positive margins mean the fight against cancer begins. Finally, loss of the tumor suppressor **p53** hallmarks the genetic start of malignant transformation—p53 mutations are found in 80% of carcinomas but are almost never found in nonmalignant adenomas. It is likely no longer a polyp, but a fungating mass with invasion.

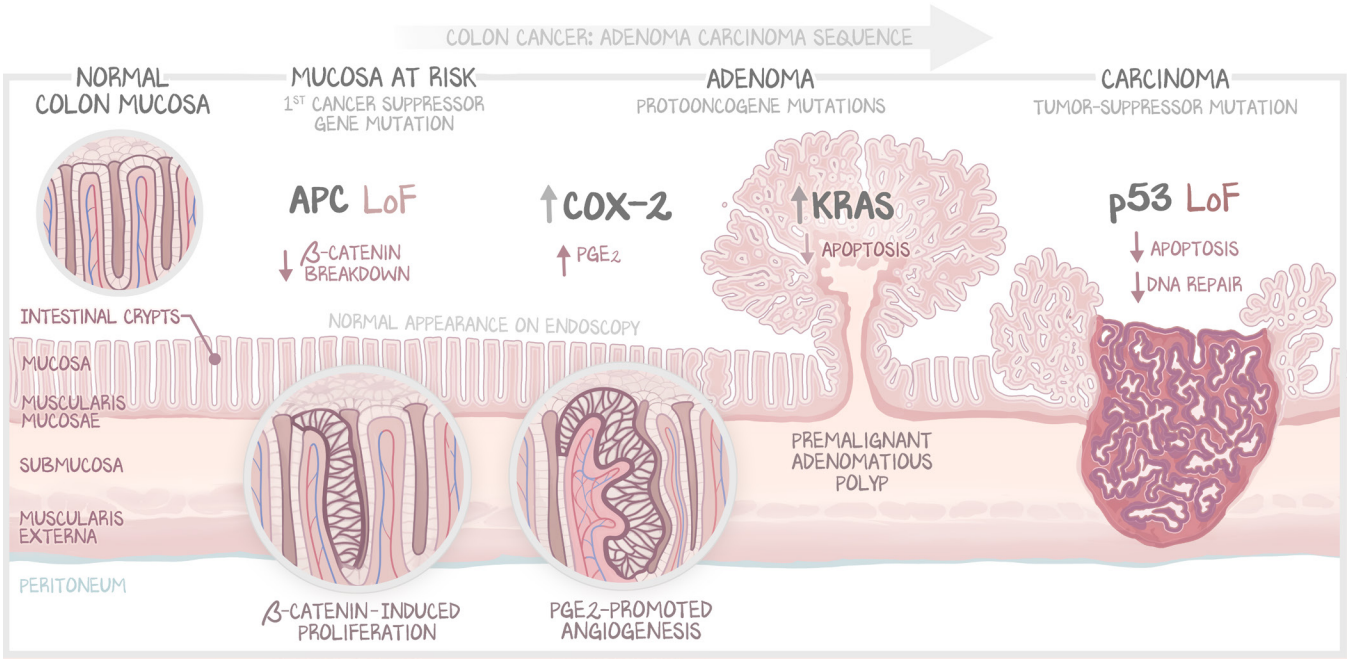

Figure 12.3: Adenoma-Carcinoma Sequence

Sporadic mutation results in the loss of the tumor suppressor APC. The β-catenin proliferation signal is disinhibited, and the cell proliferates, acquiring new mutations, such as in COX-2. Adenomas result from unregulated proliferation. By the time there is a visible adenomatous polyp, there will likely be a mutation in *KRAS*. These premalignant lesions will continue to acquire mutations. As *TP53* is lost, the cells undergo full malignant transformation into carcinoma.

This is a progression. **If given enough time, adenomas will become malignant.** If caught early in the progression (APC and COX-2 mutations, but not *KRAS* or p53), cancer is prevented. The adenoma-carcinoma sequence is how cancer develops from sporadic mutations (i.e., in the general population) and the familial adenomatous polyposis syndromes. The adenoma-carcinoma sequence tends to cause left-sided colon cancer.

Microsatellite Instability (MSI) Pathway

Having "pathway" in the name implies that microsatellite instability is part of the pathway. It isn't. **Microsatellites** are repeated sequences of noncoding DNA and are, therefore, not genes. They are neither proto-oncogenes nor tumor suppressor genes. But they are surrogates for how well DNA is being conserved, as microsatellites are typically extremely well-conserved in mitosis. Microsatellites are said to have stability in normal cells because they don't change with divisions. Their **instability** is an indication that the DNA mismatch-repair genes are faulty. The microsatellites don't cause the cancer; they are just a genetic marker that something else is broken. **MLH1** and **MSH2** are DNA mismatch-repair enzymes that we studied in Biochemistry: DNA to Protein #6: *DNA Synthesis Repair*. They are back now to cause colon cancer. Colon cancers that develop through the MSI pathway will progress through a phenotype that demonstrates **sessile** serrated adenomas. MSI pathway malignancies are typically right-sided colon cancers. With mismatch-repair genes failing to maintain DNA integrity, certain vulnerable genes mutate. The genes implicated are those that upregulate growth, such as TGF-β and ***BRAF***. *BRAF* is part of the MAPK arm of the RET receptor, whereas *KRAS* is part of the PI3K arm of the RET receptor. Both are common targets for malignant transformation. We will demonstrate this concept in Endocrine but want to plant the seed now. Ultimately, MSI cancers demonstrate loss-of-function mutations in ***BAX*** (which lead to evasion of apoptosis).

Very specifically, *KRAS* and *TP53* mutations are not found in MSI pathway cancers.

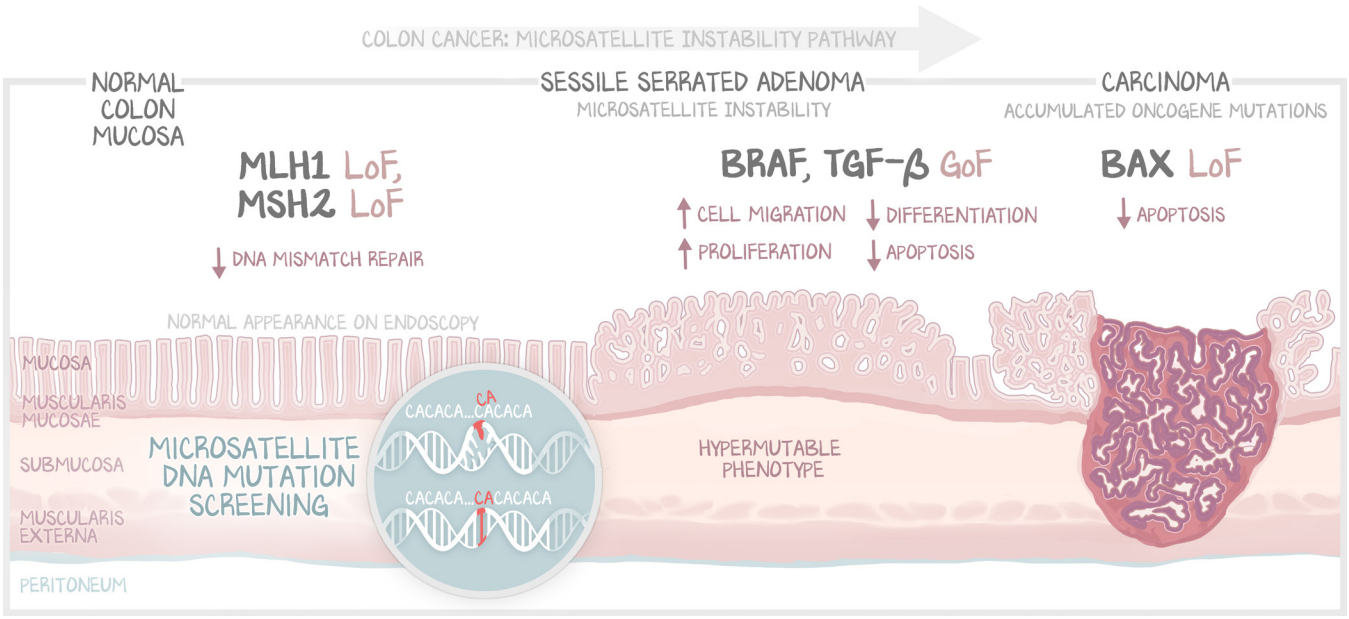

Figure 12.4: Microsatellite Instability Pathway
The loss of DNA mismatch-repair enzymes results in the accumulation of mutations. As *BRAF* gain of function is acquired, the sessile adenoma forms. The loss of DNA repair enzymes combined with unregulated proliferation results in the accumulation of malignant genes, often in *BAX*, TGF-β, or both.

Familial Syndromes

Familial adenomatous polyposis is caused by an inherited ***APC* mutation** on chromosome 5. The loss-of-function of tumor suppressors is usually autosomal recessive—**FAP is autosomal DOMINANT**. In sporadic mutations following the adenoma-carcinoma sequence, APC is lost in one cell. That one cell makes a polyp by proliferating and accumulating new mutations. Over ten years, that one cell can transform into cancer. These sporadic mutations happen infrequently—of the billion cells replaced in the colon each day, most humans only develop a few polyps, if any, in their lifetime. In order to start the adenoma-carcinoma sequence, APC's function must be lost. This is why colon cancer first appears in the 40s and 50s—enough time has to pass for one cell to sporadically acquire the APC mutation AND THEN the polyp starts to grow and accumulate more mutations. Now, imagine what would happen if **every cell in the colon already had the APC mutation . . . at birth**. That means every cell in the colon, from birth, would have already started the adenoma-carcinoma sequence. That means there would be many polyps and many polyps that happen early. And every single cell has a predisposition for malignant transformation. And that is precisely what happens. FAP presents with **thousands of adenomatous polyps** in the teenage years. Every polyp is nonmalignant but has the chance to become malignant. With so many polyps growing, without intervention, there will be a malignant transformation in the 20s and death in the 30s. If a colonoscopy were performed, all that would be seen is adenomatous polyps. The **entire colon** is affected. Only one or two may have a malignancy in them at the time of the scope. But how to know which one? How can you be sure? The only way to be sure is to take them all, which is why a **prophylactic colectomy** is indicated.

There are two variants of the traditional FAP—Turcot's and Gardner's syndromes. **Turcot's** syndrome (turban syndrome) is FAP + CNS tumors. A "turban" is worn on the head, which helps cue you to remember the CNS tumors. **Gardner's** syndrome is FAP + bone and soft tissue tumors. *FAP is the original, with only colon involvement; Turcot's is FAP with a turban, and Gardner's is FAP that has skin findings and osteomas.*

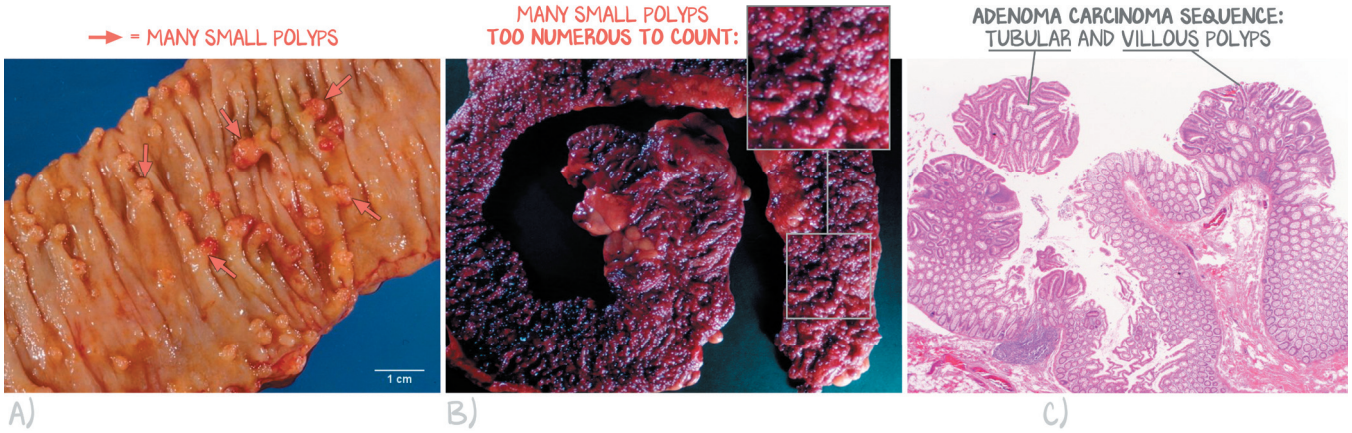

Figure 12.5: FAP Polyps
(a) Early in disease, the polyps are small and numerous but do not occupy the entirety of the mucosa. (b) If not resected, the entirety of the colonic mucosa becomes polyps, many of them gaining malignant transformation before the teenage years. (c) FAP follows the adenoma-carcinoma sequence and therefore presents with tubular, villous, and tubulovillous adenomas; however, there are many more than in cases of sporadic mutation.

Hereditary nonpolyposis colorectal cancer (HNPCC), also called **Lynch syndrome**, is caused by **DNA mismatch-repair enzyme** deficiency. It follows the microsatellite instability pathway. It was named "non-polyp-osis" because the cancer arose in mucosa without obvious pedunculated adenomatous polyps. But we now know that they are serrated sessile polyps, so "nonpolyposis" is a bit of a misnomer. It is also transmitted in an **autosomal dominant** inheritance pattern. HNPCC presents with **right-sided colon cancer**. DNA mismatch is a problem for any cell that proliferates, and the mutation is inherited by all cells. Patients with HNPCC are at risk for other cancers, specifically **ovarian**, **uterine**, and **stomach** cancers (there are many others, but these are the associations to remember). Look for a clustering of cancers in families, and use the 3-2-1 rule: 3 family members affected, spanning at least 2 generations (2 first-degree relatives involved), and at least 1 cancer found before age 50.

Nonmalignant Polyps

Hyperplastic polyps. Hyperplastic polyps are benign epithelial proliferations. They are found on screening colonoscopies, especially in the 60s and 70s. They have no symptoms, do not bleed, and do not progress to cancer. They are thought to result from decreased epithelial cell turnover and delayed shedding of surface epithelial cells, resulting in a "piling up" of goblet cells and absorptive cells on the mucosa surface. Because they pile up, they raise the mucosa into the lumen. Their chief significance is that they look like sessile premalignant polyps to an endoscopist, so they need to be removed and reviewed by a pathologist. The risk of the procedure is low, but not zero. The patient's advanced age makes the decision to go in again, as one should do if polyps are found, a challenge. They are generally small nodules, often on crests of mucosal folds. Histologically, there are epithelial cells and goblet cells only, no dysplasia, but there is often serration. Both the features, "sessile" and "serrated," sound like malignancy. But they are normal cells and lack any mutations associated with either pathway.

Peutz-Jeghers = Hamartomatous polyps. Presenting around age 10–15, a patient will present with dark spots on the lips, mouth, and genitalia (called **mucocutaneous hyperpigmented macules**). If endoscopy is performed, hamartomatous polyps will be found in the intestine. Hamartomatous polyps are pedunculated and characterized by disorganized growth of the muscularis mucosae and epithelium. They are benign. Peutz-Jeghers syndrome is an **autosomal dominant** disorder but is exceedingly rare. Although the polyps aren't cancerous, these patients are at an exorbitantly increased risk for other malignancies. At birth, testicular cancer; in late childhood, gastric and small intestine cancers; in the 20s and 30s, just about everything—colon, pancreatic, breast, lung, ovarian, and uterine.

Sporadic hamartomatous polyps are usually singular, can be found anywhere in the GI tract, and are entirely benign.

Clinical Colon Cancer

Risk factors for colon cancer include a diet that is low in fiber and high in red meat, smoking, family history (even in exclusion of the known genetics above), and age. The highest incidence of colorectal cancer is in those in their 60s and 70s, although new data suggest that we should be screening sooner to catch malignancies developing in the 40s. Colon cancer tends to metastasize hematogenously through the portal system and thus to the liver. Although colon cancer is a carcinoma, and carcinomas usually spread through lymph, the direct blood supply to the liver from the GI tract through the portal vein causes the liver to act as a filter for any metastases that make it to the vasculature.

Clinically, we can separate the presentation into left-sided and right-sided colon cancers.

Right-sided cancer is the more dangerous cancer. Because stool is softer on the right (water has not yet been absorbed), this cancer does not cause obstruction, so the patient has no complaints. The polyps can get large and ulcerate, releasing microscopic amounts of blood into the stool. This presents with a fecal

occult blood test (FOBT)-positive stool that prompts the colonoscopy. Right-sided lesions usually grow as a sessile raised lesion. The bleeding may lead to iron deficiency anemia. A postmenopausal female or any male with iron deficiency anemia has colon cancer until proven otherwise.

Left-sided cancers produce a thickened wall and a narrowed lumen—a stricture. This causes obstruction. As the feces backs up, it gets stuck until it is shot through as diarrhea. Thus, alternating constipation (obstruction) and diarrhea (forces its way through) are indicative of left-sided cancer. Likewise, a change in the caliber of the stool to **pencil-thin** stools is suggestive of a stenotic colon. A left-sided cancer is called a **napkin-ring tumor**, as it mimics the behavior of a napkin ring at a restaurant, encircling and constricting the lumen. A **barium enema** will reveal the stenosis, termed an **apple-core sign.**

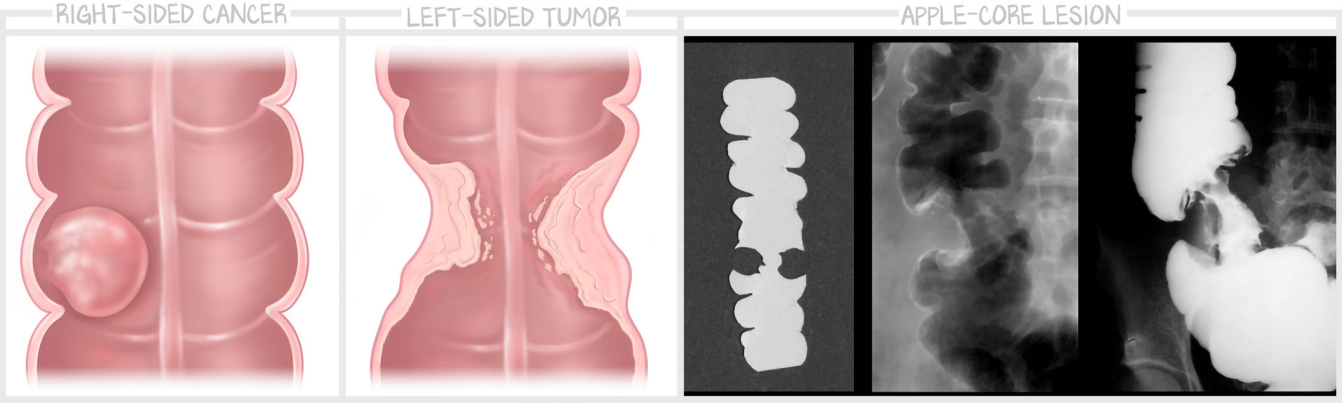

Figure 12.6: Clinical Colon Cancer
An illustration of a right-sided colonic lesion, a raised sessile mass, compared to an illustration of a left-sided tumor. The finding of an apple-core lesion is a late-stage finding, indicative of the cancer invading the lumen. Different examples of an apple-core lesion are shown in the radiographs to the right. The example in the rightmost barium enema is from the same patient as that in the non-contrasted CT to the left of it.

Patients should be screened for colorectal cancer and not be diagnosed with cancer until after it has progressed to the point of symptoms.

Screening for all patients begins at age 50. The options are **colonoscopy q10y**, **FOBT q1y**, or **flex sig q5y with FOBT q3y**. The colonoscopy allows the visualization of the colon, removal of polyps, and definitive diagnosis, but the operator may miss a small polyp. Fecal immunochemical testing (FIT) is the new fecal occult blood test (FOBT). Although FIT is technically better, you should not be asked to choose between them and should learn them as the same thing—testing poop for blood. The flex sig option is done in resource-limited areas. The flex sig only sees the sigmoid colon and relies on the FOBT to capture the right-sided lesions. Flex sigs do not require a colon prep or a gastroenterologist to perform. The gold standard for screening is a colonoscopy.

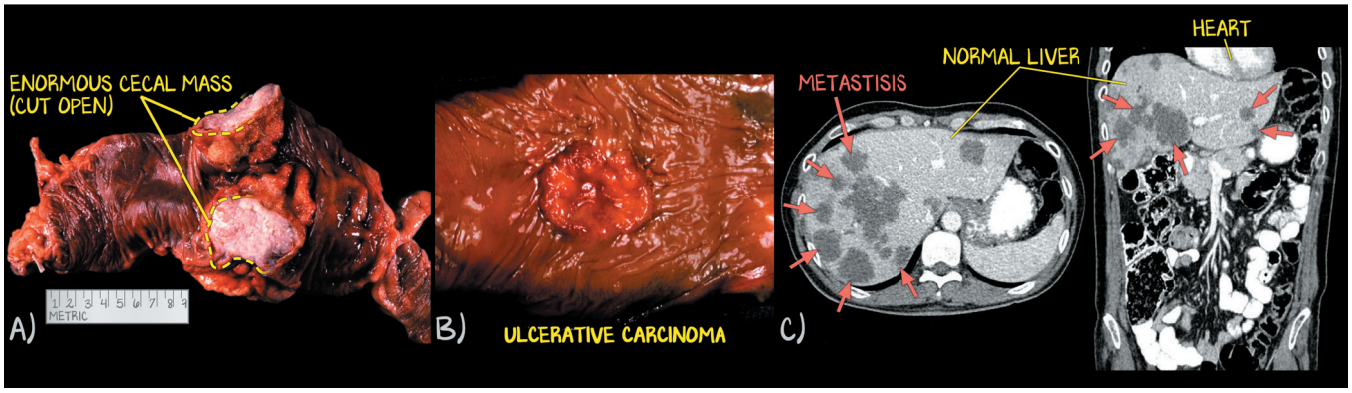

Figure 12.7: Colon Cancer
(a) Gross autopsy sample showing a large ulcer that has been dissected to reveal the mucosa. The firm pink nodules are the cancer. This is near the cecum, though the cancer has destroyed the recognizable bowel. (b) Ulcerative colon adenocarcinoma showing heaped-up margins. It is red due to hemorrhage. (c) Should colon cancer metastasize, the first place it is found is the liver, the metastasis traveling within the portal circulation.Screening begins sooner for some people. If **a first-degree relative** had colon cancer, the patient should start screening at 40, or **10 years prior to the age of the relative's diagnosis**, whichever is earlier. Patients with **ulcerative colitis** have an alternative mechanism for malignant transformation, mitigated by their chronic inflammation. Prophylactic colectomy is curative. CRC screening begins **8 years after the diagnosis of UC** and must be performed **annually**.

Carcinoembryonic antigen (CEA) is a blood test. CEA is not a screening tool. CEA is not a diagnostic tool. CEA is used in someone who has already been diagnosed with colon cancer who is going to receive treatment. The CEA can be tracked to assess recurrence and response to therapy. It has no other clinical use.

Anal Cancer

The anus is not endoderm-derived. It is ectoderm-derived and lined with stratified squamous cells. Remember that little strip of nonkeratinized stratified squamous epithelium at the anal transition zone, the pectinate line? Yep. That is where anal cancer develops. Anal cancer is, therefore, a **squamous cell carcinoma**. And just like squamous cell carcinoma of other nonkeratinized stratified squamous epithelium (larynx, esophageal, cervical), it is caused by **HPV**. HPV goes where semen goes. Those with HIV and especially AIDS are at even more increased risk.

HPV doesn't disseminate through the bloodstream. The single greatest risk factor is unprotected anal receptive sex. This consequence of sexual behavior does not discriminate against biological sex or sexual orientation. In fact, in 2019, more women were diagnosed than men. But routinely on licensing exams, men who have sex with men are used to represent those likely to engage in anal intercourse. The highest incidence of anal cancer on licensing exams is in **men who have sex with men.**

Anal cancer is **exquisitely sensitive to chemotherapy**, extremely unlike colorectal cancer, which is why it is so important to distinguish it.

Intestinal Carcinoid

Carcinoid tumors occur in the lungs and intestines. Carcinoid tumors release serotonin. Serotonin is degraded by the lung and the liver. When carcinoid tumors are in the colon, before they metastasize, the portal circulation carries the serotonin to the liver where it is degraded, so no serotonin syndrome is felt. After they metastasize to the liver, the serotonin they release no longer gets cleared by first-pass metabolism, so serotonin is allowed to escape into the inferior vena cava. If the carcinoid is in the lung or adrenal gland, there is no liver or lung distal in the circulation to clear the serotonin, so the symptoms are felt immediately. When in the colon, the cancer must first metastasize to the liver before symptoms can be felt. The syndrome is **flushing, cramping, nausea, vomiting, diarrhea,** and **fibrosis of the heart valves**. When it comes from the lung, the left heart is affected. When it comes from the colon/liver, the **right heart is affected**. The lungs degrade the serotonin, so the left heart is unaffected. It is diagnosed by the presence of **5-HIAA in the urine**, a product of serotonin metabolism. These are incredibly indolent. They are difficult to cure. But life expectancy, despite metastasis, remains good.

Citation

Figures 12.1, 12.7a, 12.7b: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.

Figures 12.2, 12.5: Courtesy of Webpathology.

Figures 12.6c, 12.7c: Courtesy of Radiopaedia.